REMARKS

Claims 1-28 are in this application.

Claims 24-25 and 27-28 are withdrawn.

Claims 29-30 have been cancelled.

Information Disclosure Statement

A copy of the AR reference Hamada, M., et al. "Effects on RNA Interference in Gene Expression (RNAi) in Cultured Mammalian Cells of Mismatches and the Introduction of Chemical Modifications at the 3'-Ends of siRNAs." Antisense and Nucleic Acid Development 12:301-309 (2002) is included with the Information Disclosure Statement being filed with this response.

Alleged Rejections under 35 USC 102 and 35 USC 103

Claims 1-23 and 26 are rejected under 35 U.S.C. 102(e) as being anticipated by Zamore, et al. (US 2005/0186586 cited on PTO Form 892 mailed January 24, 2008) as evidenced by Aravin, et al. (Development Cell. 2003 cited on PTO Form 892 mailed January 24, 2008) and Elbashir, et al. (Nature 2001 cited PTO Form 892 mailed January 24, 2008.

The Examiner has rejected claims 1-23 and 26 as being anticipated by Zamore et al. (US *2005/0186586).* The Examiner asserts that the claimed dsRNA is disclosed in Fig. 6A of Zamore et al. This is respectfully traversed.

The claimed dsRNA is defined as being capable of suppressing the expression of a target gene in a cell by RNAi, which is generally called "siRNA," and is defined as being designed such that the dsRNA contains a mismatch(es) between sense and antisense strands thereof.

On the other hand, Fig. 6A of Zamore et al. discloses the dsRNAs consisting of miRNA and the opposite strand thereof, which are deduced to be generated by Dicer cleavage of

naturally-occurring miRNA precursors (paragraphs [0019] and [0287] of Zamore et al.). The term "siRNA" found in paragraph [0019] means an siRNA-like duplex which may be formed if the miRNA precursor is cleaved by Dicer into an siRNA duplex-like structure, in view of paragraph [0287]. Therefore, Fig. 6A of Zamore et al. discloses miRNAs, not siRNAs.

As disclosed in paragraph [0003] of Zamore et al. siRNA and miRNA commonly trigger post-transcriptional gene silencing, but belong to different types of RNA generated by different processes. Further, the miRNA has been known to control the translation of a target gene, and to be different from the siRNA in that it causes gene silencing with no degradation of the target mRNA (see, for example, page 6877, the right column, the 3rd paragraph of Elbashir et at., EMBO Journal, Vol 20, No. 23, pp .. 6877-6888, 2001, which is cited by the Examiner in the outstanding Action). Please note that the term "stRNA" (small temporal RNA) found in Elbashir et al. means miRNA (see, for example, paragraph 0080 of Zamore et aL). Therefore, miRNAs are clearly distinguished from siRNAs in the developments and functions thereof.

Accordingly, Fig. 6A of Zamore et al. does not disclose siRNA, i.e., dsRNA which is capable of suppressing the expression of a target gene in a cell by RNAi. In addition, the Examiner's attention is drawn to the fact that the dsRNAs disclosed in Fig. 6A of Zamore et al. are deduced to be generated by Dicer cleavage of. naturally-occurring miRNA precursors (paragraphs [0019] and [0287] of Zamore et al.). Therefore, the mismatches found between sense and antisense strands of the dsRNAs are to be generated naturally, but not artificially introduced (designed). Accordingly, Fig. 6A of Zamore et al. does not disclose dsRNA which is designed such that the dsRNA contains a mismatch(es) between sense and antisense strands thereof as included in independent claims 1 and 11. Thus it is clear that the claimed dsRNA is not disclosed in Fig. 6A of Zamore et al.

Anticipation requires that each and every element of the claimed invention be disclosed in a single prior art reference. *In re Paulsen*, 30 F.3d 1475, 31 USPQ 1671 (Fed. Cir. 1994). For anticipation, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ2d 1001 (Fed. Cir. 1991). Therefore, as alll elements of the claims are not disclosed in the cited reference, claims 1-23 and 26 are not anticipated by Zamore et al.

It is respectfully requested that the rejection be withdrawn.

Claims 1-23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jayasena, et al. (US 2004/0248299), Khvorova, et al. (US 2007/0031844), Elbashir, et al. (EMBO Journal 2001, Vo. 20, No. 23: 6877-6888) and Holen, et al. (Nucleic Acids Research 2002, Vol. 30, No. 8: 1757-1766). This is respectfully traversed.

The Examiner states that Jayasena et al. and Khvorova et al. disclose that the strands of the siRNA are more efficiently loaded into RISC when the ends are more weakly associated. Further, he states that it was well known in the art that mismatched base pairs decrease the stability of a duplex. Therefore, the Examiner asserts that those skilled in the art would have wanted to incorporate mismatches at the ends of the siRNA (page 9, line 19 to page 10, line 3).However, it is well known in the art that a single stranded RNA is more susceptible to degradation by RNase than a double stranded RNA. If the siRNA contains. a single stranded structure at its end due to the presence of mismatches, the siRNA would be expected to be easily degraded by RNase in a cell, resulting in very low efficiency of RNAi. Therefore, those skilled in the art would never try to incorporate a mismatch(es) into siRNA molecules.

In fact, those skilled in the art have recognized it very important to prevent degradation of siRNA in a cell for designing an efficient siRNA. For example, Elbashir et al.

discloses "(t)he siRNA user guide" on page 6885, the left column, and describes that the RNase resistance is preferred property of siRNA in the first paragraph of the guide. Elbashir et al. describe in the same paragraph that efficiently silencing siRNA duplexes must be selected to form a 19 bp double helix with 2 nt 3'-overhanging ends. It should be noted that the term "double helix" means a region composed of completely matched base pairs usually. Therefore, those skilled in the art would not conceive to incorporate a mismatch(es) into siRNA molecules.

The Examiner also relies upon Elbashir et a1. and Holen et a1. in this rejection. He believes that Elbashir et a1. and Holen et a1. disclose effect of mismatches introduced into siRNAs on RNAi. Elbashir et at and Holen et a1. do not disclose a mismatch(es) between the sense strand and the antisense strand of siRNA. The mismatches disclosed in Elbashir et al. and Holen et al. are between the antisense strand of siRNA and the target mRNA.

Elbashir et a1. refers to mismatches on page 6884, the paragraph bridging left and rightcolumns. In this paragraph, sequence changes are introduced into the paired segments of siRNA in order to examine the sequence specificity of target recognition. In the same paragraph, they describe that the sequence changes in one siRNA strand were compensated for in the complementary siRNA strand to avoid disturbing the base-paired siRNA duplex structure. Therefore, the mismatches disclosed in this paragraph are between the antisense strand of siRNA and the target mRNA. Elbashir et al. also refers to mismatches on page 6885, the paragraph bridging left and right columns. This paragraph relates to the target recognition, i.e., the recognition of target mRNA by siRNA. In particular, this paragraph describes that siRNA duplexes may be able to discriminate mutant or polymorphic alleles in gene targeting experiments.

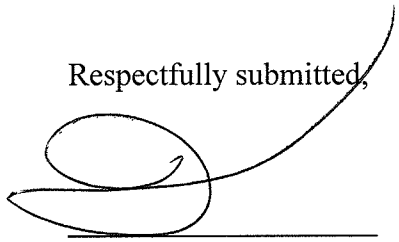
In order to discriminate mutant or polymorphic alleles, siRNA should have a mismatch(es) relative to the target mRNA, not between the sense strand and the antisense strand of the siRNA. Therefore, the mismatches disclosed in this paragraph are between the antisense strand of siRNA and the target mRNA.

Holen et al. discloses dsRNA containing either one or two mismatches relative to an mRNA, as suggested by the Examiner. It is clear that the mismatches disclosed in Holen et al. are between the antisense strand of siRNA and the target mRNA.

Accordingly, Elbashir et al. and Holen et al. do not provide any teaching for a mismatch(es) between the sense strand and the antisense .strand of siRNA, which is introduced into the claimed dsRNA. Therefore, the rejection should be withdrawn.

It is submitted that the application is in condition for allowance and favorable consideration is respectfully requested.

Respectfully submitted,



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